REMARKS

This Amendment is being filed in response to the Office Action mailed on March 9, 2007.

On page 2 of the Office Action the Examiner rejected claims 20-22 under 35 U.S.C. § 112, second paragraph.

Reconsideration is requested.

Claims 20 and 22 have been canceled. Therefore, the rejection with regard to these claims is rendered moot. Claim 21 has been amended to be dependent on claim 1. Therefore, it is requested that the 112, second paragraph rejection be withdrawn.

On pages 2-3 of the Office Action the Examiner rejected claims 1, 3-6, 8, 9, 12, 13, 17-20, 27, 28, 30-32 and 64 under 35 U.S.C. §102(e) as being anticipated by United States Patent No. 7,022,342 (hereinafter "Chen et al.").

Reconsideration is requested.

Submitted herewith is a Rule 131 Declaration by Samuel Yuk, one of the named inventors in the present application, stating that the claimed invention was made prior to March 28, 2002. Applicants submit that March 28, 2002 is the earliest effective filing date for the Chen et al. reference and therefore Applicants have overcome the 102(e) and 103(a) rejections with regard to Chen et al.

On pages 3-5 of the Office Action the Examiner rejected claims 1, 3-6, 8, 9, 12, 13, 17-23, 27-49,51-54, 56, 57 and 60-64 under 35 U.S.C. §103(a) as being unpatentable over Chen et al. in view of WO 99/61005 (hereinafter "Sriwongjanya et al.").

On pages 5-6 of the Office Action the Examiner rejected claims 7, 10, 11, 14-16, 24-26, 49, 55, 58 and 59 under 35 U.S.C. §103(a) as being unpatentable over Chen et al. in view of United States Patent No. 6,569,463 (hereinafter "Patel et al.").

Reconsideration of the above rejections is respectfully requested.

As recited above, Applicants have submitted herewith a Rule 131 Declaration by Samuel Yuk that states that the present inventors made the claimed invention prior to March 28, 2002. Additionally, Applicants affirmatively state that Chen et al. (U.S. Pat. No. 7,022,342) and the present application were commonly owned at the time the invention was made. At the time the presently claimed invention was made said invention was subject to common ownership of United States Patent No. 7,022,342.

United States Patent No. 7,022,342 was and is currently owned by Andrx Pharmaceuticals, LLC. See December 18, 2002 merger document recorded with the USPTO at Reel/Frame 013791/0473. The present application is also currently assigned to Andrx Pharmaceuticals, LLC (See Reel/Frame 014283/0806).

Therefore it is requested that the 103(a) rejections with regard to Chen et al. are improper in due to 35 U.S.C. §103(c).

Additionally, Chen et al. is directed towards dosage formulations containing propranolol hydrochloride. Propranolol is a different chemical compound than metoprolol. Further, even if they were the same compound, hydrochloride salts of one drug have different chemical and physical properties from succinate salts of the same drug. Additionally, the Chen et al. reference does not disclose the use of channeling agents. The passage cited by the Examiner only teaches that "[a] suitable filler should have a particle size of about 20 μm (microns)" (see Chen et al. at col. 4, lines 48-54). Chen et al. then lists several possible filler, some of which the present application lists as possible channeling agents. However it is well known in the art that many excipients can have multiple functions. The function an excipient performs is usually dependent on the amount of the excipient, the location of the excipient in the formulation and the type of formulation. The recitation in Chen et al. is only directed towards the use of the cited excipients as filler and therefore cannot be interpreted to teach the use of channeling agents. Therefore, the Chen et al. reference does not disclose or suggest to one skilled in the art how to make a controlled release dosage form containing metoprolol succinate.

Therefore it is requested that the 102(e) rejection with regard to Chen et al. be withdrawn.

On pages 7-9 of the Office Action the Examiner rejected claims 1, 3-9, 14-49, 5-57 and 60-64 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 6,733,789 (hereinafter "Stark et al.") in view of U.S. Pat. No. 6,190,692 (hereinafter Busetti et al.) and Sriwonjanya et al. WO 99/61005.

On pages 9-10 of the Office Action the Examiner rejected claims 10-16, 58 and 59 under 35 U.S.C. § 103(a) as being unpatentable over Stark et al. in view of Busetti et al. and Patel et al.

Reconsideration is requested.

In order to appreciate the patentability of the present claims a brief discussion of the prior art metoprolol formulations is required. United States Patent Nos. 4,957,745 (the '745 patent) and 4,927,640 (the '640 patent) teach controlled release dosage forms that employ insoluble cores for delivering metoprolol or a pharmaceutically acceptable salt thereof. The '745 and '640 patents only teach the use of insoluble cores because the combination of water soluble materials with metoprolol caused an increase in the osmotic pressure that led to the bursting of dosage forms and premature dumping of the drug (see present application page 1, last paragraph).

The '640 patent is explicit in requiring the use of water insoluble cores, namely those that are "not soluble in water, physiological fluid or in common liquids used for intravenous infusion" (col. 2, lines 45-48). Further, the cores must have "a high degree of purity, that is, free from soluble contaminating compounds" (col. 2, lines 57-59). Additionally, the invention disclosed in the '640 patent "contain[s] a high percentage of active ingredient and are not contaminated by soluble inert compounds" (col. 3, lines 45-48).

The '640 patent teaches that:

> As can be seen from the figure a controlled and almost constant release of the active compound was obtained, when the active compound was applied on silicon dioxide or glass, whereas a core of soluble sodium chloride resulted in a considerably higher initial release rate, which also is illustrated in FIG. 2 (Reference 2 below) where soluble potassium chloride was used as core material.

(See col. 5, lines 29-36).

Table 1 of the '640 patent clearly shows that two reference examples employing NaCl and KCl as core material (both of which are water soluble) resulted in a very rapid release of metoprolol. This type of release is not consistent with the controlled release required of a once a day beta blocker.

Additionally, the use of the insoluble cores necessitated the use of organic solvents such as methylene chloride to coat the cores. This leads to increased production costs due to manufacturing, regulatory and environmental difficulties.

Applicants have surprisingly discovered a metoprolol dosage form that overcomes these problems and employs metoprolol coated water soluble/water swellable cores. The present invention solves the problems associated with metoprolol formulations through

the novel use of a combination of excipients, water soluble/water swellable cores, and controlled release coatings.

The Stark et al. reference is not directed towards controlled release dosage forms that deliver metoprolol or a pharmaceutically acceptable salt thereof, and therefore was never intended to solve the problems associated with the delivery of metoprolol using water soluble excipients. Specifically, the specification of the Stark et al. reference is directed towards formulations containing bisoprolol, and does not mention the use of metoprolol. While bisoprolol is in the same class of drugs as metoprolol it does not have all the same physical properties and therefore would not act exactly the same way in a particular formulation. While Applicants agree that many of the excipients recited in the claims of the present application are listed in the Stark et al. reference, Applicants submit that there is no teaching in the Stark et al. reference that would allow one to produce a controlled release metoprolol pellet with a water soluble/water swellable core without undue experimentation.

Further, the release profile recited in Stark et al. is different from the release profile recited in claims 31-32 and 35-48. Specifically, the release profile described in Stark et al. is measured using USP 2 Apparatus in phosphate buffer at pH 6.8 at 37°C and 50 rpm. The claimed release profile in the present application is measured using USP Type 2 apparatus, at 75 rpm, 37°C and in a phosphate buffer medium with a pH of 7.5. Also, the release described in Stark et al. recites "(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus; (b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and (c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus". In contrast the claimed release in the present application recites "0-40% of the metoprolol is released after 2 hours; 5-50% of the metoprolol is released after 4 hours; 25-80% of the metoprolol is released after 8 hours; not less than 50% of the metoprolol is released after 16 hours." Bisoprolol is a different chemical entity than metoprolol with different chemical and physical properties, most importantly for the present discussion, these compounds have different solubilities. Additionally, the different salts of these base drugs also have different solubilities (the fumarate salt is disclosed in the Stark reference, whereas the succinate salt is claimed in the present application). Therefore, teachings regarding one compound (in a different salt form) do

not instruct one skilled in the art on how to make controlled release dosage forms using different drugs in different salt forms.

Sriwongjanya et al. does not cure the deficiencies that exist in the Chen et al. reference and therefore does not render the claims of the present application obvious. Specifically, Sriwongjanya et al. (like Stark et al.) is not directed towards controlled release dosage forms comprising metoprolol and water soluble/water swellable cores.

Sriwongjanya et al. discloses oral controlled release dosage formulations containing an analgesic, and more specifically, controlled release dosage formulations containing tramadol. Further, the cores of the dosage forms disclosed in the Sriwongjanya et al. reference are prepared using wet granulation techniques that produce homogenous cores containing the pharmaceutical agent. In sharp contrast the present invention employs coating the metoprolol (and additional excipients) onto the inert water soluble/water swellable cores. These are wholly different procedures.

Busetti et al. is directed towards controlled release dosage forms. However, there are no examples in Busetti et al. that are directed towards metoprolol (or bisoprolol). Further, Busetti et al. does not teach the equivalency of metoprolol and bisoprolol, it only teaches that they are both beta blockers. All of the dosage forms taught in Busetti et al. are either granulations or liquid encapsulations. There is no instruction with regard to water soluble or water swellable cores anywhere in the reference. Therefore, Busetti et al. does not teach that it would be possible to develop a controlled release dosage form using metoprolol succinate and a water soluble/water swellable core.

Patel et al. also does not cure the deficiencies that exist in the Stark et al. reference and therefore does not render the claims of the present application obvious. Specifically, Patel et al. is not directed towards controlled release dosage forms comprising metoprolol. While Applicants agree that the specification of Patel et al. does recite that "metoprolol" is a drug that may be employed in the Patel et al. formulations, metoprolol is only one of hundreds of drugs listed in the specification. Further, there are no specific examples directed towards metoprolol. Also, the use of sugar as a substrate is merely recited in a list of possible substrates (Patel et al. is practically a dictionary of possible excipients that can be used in pharmaceutical preparations). The critical factor is that there is absolutely no direction in Patel et al. to make a controlled release dosage form comprising metoprolol employing a water soluble/water swellable core.

It is therefore requested that the above 103(a) rejections be withdrawn.

Based upon the above remarks, amendments, request for continued examination and Declaration under 37 C.F.R. 1.131. Applicants respectfully submit that Claims 1, 3-49 and 51-64 are allowable and that the present application is in proper form for allowance.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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